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The Total Synthesis of Taxamairin B

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Abstract: *Taxamairin B, a novel rearranged 9(10→20)-abeo-8,11,13-triene diterpene, has been synthesized by a short and efficient route. A friedal-Crafts annunation and the oxidation of the allylic and benzylic methene group are the key steps.*

The rearranged 9(10→20)-*abeo*-abietane diterpenoids, a rare structural type of diterpene thought to arise from the rearrangment of the more familiar abietane[1], have received considerable attention in the last few years[2]. The total syntheses of some of them have been reported[3,4]. Taxamairin A(**1**), B(**2**) have been isolated from the bark of *Taxus mairei Lemee et* Levl. S. Y.[5]. Many laboratories have been devoting to synthesize them, but the encouraging result has not been appeared. As a part of our synthetic studies on the naturally occuring diterpenes, we have been searching for a synthetic route to them. Herein we wish to report the first synthesis of Taxamairin B.

Our synthetic strategy, derived from the retrosynthetic analysis (scheme I), was outlined in scheme II. Ketone **3** would be a key synthetic intermediate, because it contains the entire carboncylic framework of taxamairin B and it is easy to introduce the carbonyl group at $C_{(7)}$ and the double bonds at $C_{(1)}$-$C_{(2)}$ and $C_{(10)}$-$C_{(20)}$. Accordingly, we first aimed at searching for an efficient means to prepare ketone **3**.

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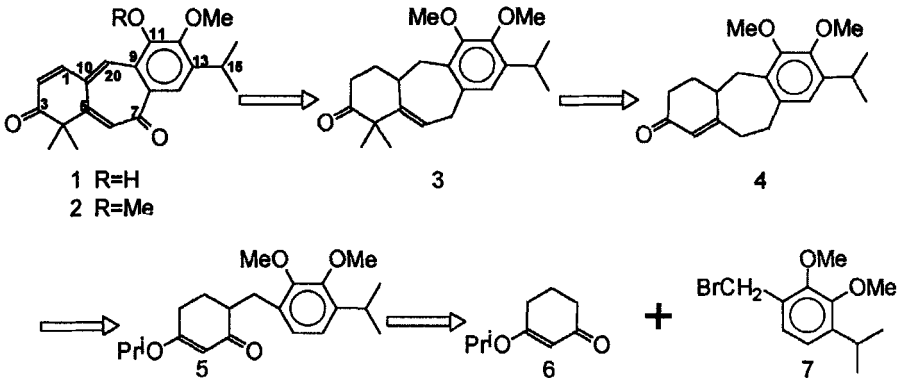
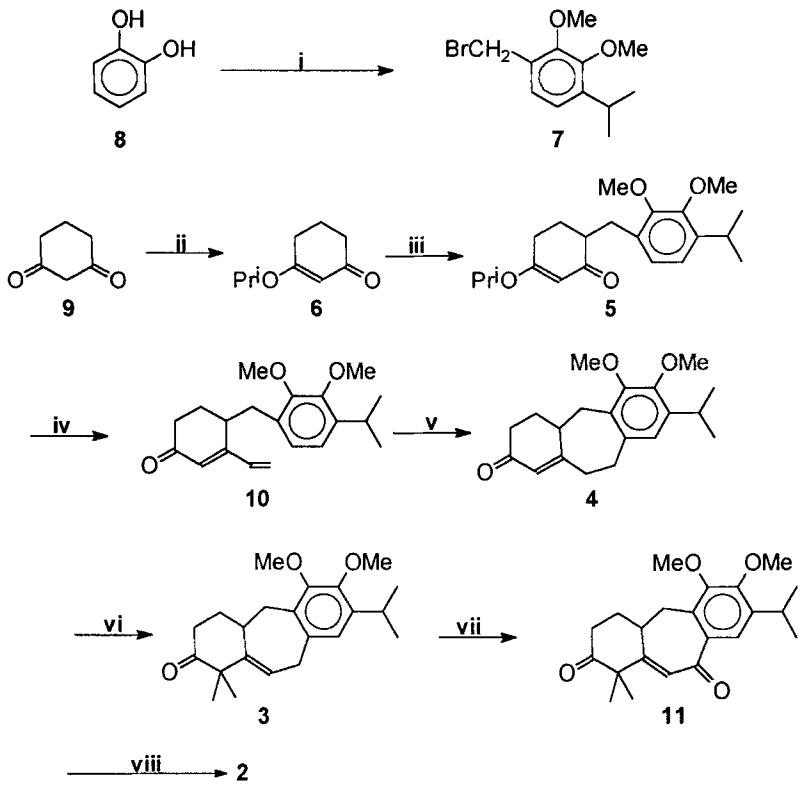


Scheme I

2,3–Dimethoxyl–4–isopropylbenzyl–2–cyclohexen–1–one **6** was readily obtained from 1,3–cyclohexandione **9** by azeotropic removal of water form a benzene / hexane / isopropyl alcohol solution in a yield of 95%[7]. Alkylation of hexenone **6** with the bromide **7**[6] in the presence of LDA was produced conveniently the coupled product **5** in 84% yield. 1,2–Addition of vinylmagnesium bromide to **5** followed by mild acid hydrolysis gave the desired cyclization precusor **10** in a yield of 89%[8].

It was reported that boron trifluoride etherate promoted the Friedal–Crafts annunation at r. t.[8], in the case of **10** it was ineffective at r. t. The annunation was completed quickly in toluene at 80–90℃ to give **4** in a yield of 73%. Alkylation of enone **4** with methyl iodide under conditions of thermodynamic control produced the desired $C_{(4)}$ geminal pairing methyl and the $C_{(4)}$–$C_{(5)}$ olefin bond moved into the cycloheptane ring product **3** in a yield of 47%. Compound **3** is a key intermediate to the target compund **2.**

By use of excess of aqueous 75% *tert*–butyl hydroperoxide and catalytic ammounts of chromic anhydride to oxidize the allylic and benzylic methene group, compound **3** was converted to the desired ketone **11** in 65% yield[10]. Heating **11** with excess of DDQ in toluene[11], followed by hydrogenation with 1eq. of hydrogen at the catalysis of 10% Pd–C resulted in the formation of the desired compound **2** in a



Scheme II

Reagents and conditions: i, Ref. 4; ii, isopropyl alcohol / hexane, Cat. PTSA; iii, 1), LDA, THF, 2), 7; iv,1), $CH_2=CHMgBr$, ether, 2), H^+, THF; v, $BF_3 \cdot Et_2O$, toluene; vi, t–BuOK, CH_3I; vii, Bu^tOOH, Cat. CrO_3,CH_2Cl_2; viii, 1), DDQ, toluene, 2), H_2. 10% Pd–C

yield of 71%. The NMR, infrared and mass spectra were identical with that of reported[5].

EXPERIMENTAL

Mass spectra were recorded on a ZAB–HS spectrometer, ^1H NMR, ^{13}C NMR, ^1H–^1HCOSY, ^1H–^1HNOESY spectra were obtained on a Bruker AM–400 instrument in $CDCl_3$ solution with TMS as an internal standard. IR spectra were recorded on a FT–170SX

spectrometer. All compounds were purified by flash chromatography(FCG) on silica gel H(200–300 mesh) made in Qingdao Marine Chemical Factory, eluting with the solvent mixture of peroleum ether and ethyl acetate.

6–(2,3–Dimethoxy–4–isopropyl)benzyl–3–isopropoxy–2–cyclohexen–1–one(5)

Under nitrogen, a solution of **6**(1.54g, 10mml) in anhydrous THF(10ml) was added dropwise to a stirring solution of LDA(prepared from diisopropyl amide(2ml) in THF(10ml) and butyllithium in ether(1.5M × 8ml) at–20℃) at –78℃, after addition, the mixture was stirred at this temperature for 1h, and warmed to r. t. and stirred for another 1.5h. Then the mixture was cooled to –78℃, a solution of **7**(2.5g, 9mmol) in THF(5ml) was added dropwise and the mixture was stirred for 2h at –78℃ and then was warmed slowly to r. t., and stirred for 20h at r. t.. The reaction was quenched with saturated ammonium chloride(10ml) at –20℃ —0℃. The mixture was extracted with ether(20ml × 5), the standard ethereal workup and followed by purification by FCG gave desired **5**(2.65g, 83.9%). MS: m / z(%) 346(48, M^+), 315(14), 304(10), 173(41), 193(100). ^{1}H NMR:δ 6.91(d, J=8.2Hz, 1H), 6.89(d, J=8.2Hz, 1H), 5.83(s, 1H), 4.45(sept, J=6Hz, 1H) 3.86(s, 6H) 3.32(m, 1H), 3.15(m, 2H), 2.51(dd, J=8.9Hz, 2H), 2.36(m, 1H), 2.06(m, 1H), 1.31(m, 6H), 1.23(d, J=6Hz, 6H). IR: υ 3065, 2961, 2934, 2861, 1674, 1609, 1380, 1273, 1109cm^{-1}.

$C_{21}H_{30}O_4$	calc	C72.80	H8.73
	found	72.86	8.72

4–(2,3–Dimethoxy–4–isopropyl)benzyl–3–vinyl–2–cyclohexen–1–one(10)

A stirring solution of **5**(3.46g, 10mmol) in THF(100ml) at 0℃ was treated dropwise with vinylmagnesium bromide(1M × 16ml) over a period of 30min. The reaction mixture was then stirred for 1.5h at r. t., then quenched with saturated ammonium chloride(25ml) at 0℃. The resulting mixture was extracted with ether(4 × 30ml), the standard ethereal workup and purification by FCG afforded **10**(2.81g, 89.5%). MS: m / z(%) 314(14, M^+), 193(100), 178(16). ^{1}H NMR:δ 6.92(d, J=8Hz, 1H), 6.87(d, J=8Hz,1H), 6.49(dd, J=17.5Hz, 10.8Hz, 1H), 6.08(d, J=17.5Hz, 1H), 5.95(s, 1H), 5.59(d, J=10.8Hz,1H), 3.88(s, 3H), 3.86(s, 3H), 3.41(sept, J=7Hz, 1H), 3.01(m, 2H), 2.73(m, 2H), 2.39(m, 1H), 1.91(m, 2H), 1.22(dd, J=6.9Hz, 6H). ^{13}C NMR:δ 200.2, 160.9, 151.2, 150.5, 141.6, 137.0, 130.8, 127.6, 125.4, 121.3, 121.0, 60.5, 60.0, 34.2, 32.9, 32.3, 26.7, 24.7, 23.6, 23.5. IR:υ 3033, 2953, 2843, 1689, 1383, 1372, 1105cm^{-1}.

$C_{20}H_{26}O_3$	Calc	C76.40	H8.33
	found	76.29	8.39

Friedel–Crafts annulation of 10

A mixture of **10**(3g, 9.6mmol) in dry toluene(100ml) was heated to 80–90℃ , and was stirred at this temperature for 4h. And then diluted with ether(500ml), washed with brine, dried over sodium sulfate, filtered and concentrated. The resulting residue was chromatographed on silica gel to provide desired **4**(2.2g, 73%). MS:m / z(%) 314(100, M^+), 299(18), 229(16), 193(42). ^1H NMR:δ 6.75(s, 1H), 5.88(s, 1H), 3.85(s, 3H), 3.82(s, 3H), 3.31(m, 2H), 2.92(m, 1H), 2.76(m, 1H), 2.72(m, 1H), 2.62(m, 1H), 2.49(m, 1H), 2.38(m, 1H), 2.27(m, 1H), 1.97(m, 2H), 1.23(t, J = 6.8Hz, 6H). ^{13}C NMR:δ 199.9, 169.1, 150.4, 148.9, 140.4, 137.2, 131.0, 125.6, 121.9. IR:υ 3028, 2963, 2857, 1679, 1386, 1381, 1109cm^{-1}.

$C_{20}H_{26}O_3$	calc	C76.40	H8.33
	found	76.49	8.35

7–Deoxy–1,2,10,20–tetrahydrotaxamairin B(3)

To sodium hydride(172mg, 7.71mmol) was added freshly distilled DMSO(4ml), the resulting mixture was warmed at 75℃ until hydrogen evolution ceased and then cooled to r. t. A solution of **4**(1.2g, 3.8mmol) in DMSO(4ml) was added to the reaction mixture. After stirring for 1.5h at r. t., the solvent was removed in vacuo. The resulting brown residue was dissolved in dry THF(30ml) and freshly distilled iodomethane(1.1g, 7.7mmol) was added. The reaction mixture was stirred overnight. Standard ethereal workup gave a yellowish residue. The residue was chromatographed to afford **3**(620mg, 47.7%). MS:m / z(%) 342(51, M^+), 327(12), 257(18), 219(31), 207(100). ^1H NMR:δ 6.71(s, 1H), 5.77(t, J = 8.1Hz, 1H), 3.89(s, 3H), 3.83(s, 3H), 3.49(m, 2H), 3.31(sept, J = 7.3Hz, 1H). 2.95(m, 1H), 2.69(m, 1H), 2.51(m, 1H), 2.47(m, 1H), 2.33(m, 1H), 1.26(s, 6H), 1.23(t, J = 7.3Hz, 6H). IR:υ 3026, 2956, 2847, 1719, 1386, 1369, 1104cm^{-1}.

$C_{22}H_{28}O_3$	Calc	C77.61	H8.2
	found	77.89	8.27

1,2,10,20–Tetrahedrotaxamairin B(11)

To a stirred solution of CrO_3(20mg, 0.2mmol) in methylene chloride(3ml) were added successively of 70% *t*–BuOOH(4ml) and **3**(500mg, 1.46mmol) in methylene chloride(2ml). The flask was closed with a plastic top. After the reaction was completed, the mixture was cooled to 0℃ , followed by addition of an aqueous 10% $Na_2S_2O_3$ solution (8ml), stirring for 1–2h at r. t., and extracted with ether(4× 25ml). The combined organic layer was washed with brine(2× 10ml), and dried over sodium sulfate. After evaporation of the solvent, the residue was purified by FCG to give **11** (338mg, 65%). MS: m / z(%) 356(45, M^+), 328(77), 313(48), 300(69),

285(100), 271(36). ^{1}H NMR:δ 7.85(1H, s), 5.86(1H, s), 3.91(3H, s), 3.87(3H, s), 3.52(2H, m), 3.33(1H, sept, J=7.3Hz), 3.18(1H, m), 2.51(1H, m), 1.31(6H, s), 1.26(6H, d, J=7.3Hz). IR: υ 3031, 2957, 2933, 2867, 1681, 1335, 1254, 1105cm^{-1}.

$C_{22}H_{26}O_4$	Calc	C 74.54	H 7.40
	Found	74.61	7.41

Taxamairin B(2)

A stirred mixture solution of **11**(300mg, 0.84mmol) and DDQ(1g, 4.36mmol) in anhydrous benzene(15ml) was refluxed for 24h. After cooling, ether (150ml)was added, and then washed with brine (4× 20ml), dried over sodium solfate. After evaporation of the solvent, the residue was dissolved in anhydrous ethanol(10ml), and catalic ammount of 10%Pd–C was added. Under hydrogen, the mixture was stirred until 1eq. of H_2 was absorbed. The catalyst was removed by filtration, and then the solvent was removed under reduced pressure. The residue was purified by FCG to give **2**(221mg, 71%). MS:m / z(%) 352(67), 337(41), 309(100). ^{1}H NMR: δ 7.91(1H, s), 7.85(1H, s), 7.28(1H, d, J=10Hz), 6.92(1H, s), 6.08(1H, d, J=10Hz), 3.95(6H, s), 3.38(1H, sept, J=7Hz), 1.41(6H, s), 1.28(6H, d, J=7Hz) IR: υ 3035, 2986, 1675, 1621, 1574, 1332, 1102cm^{-1}.

$C_{22}H_{24}O_4$	Calc	C 74.96	H 6.87
	found	75.02	6.80

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